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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/533,764	05/04/2005	William Brown	100884-1P US	6329

22466 7590 04/17/2006

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EXAMINER	
MOORE, SUSANNA	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 04/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/533,764	BROWN ET AL.	
	Examiner	Art Unit	
	Susanna Moore	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *1* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10 and 13-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *17* is/are allowed.

6)☒ Claim(s) *1-4,6,8-10,13-16 and 18-21* is/are rejected.

7)☒ Claim(s) *5 and 7* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/7/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claim 10 is objected to because of the following informalities: two species listed on page 9 (lines 9-12) are not represented by the compound of formula (I). Please remove from claims. Appropriate action is required.

Claim Rejections – 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claim 15 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "functional" is not clearly defined. By using the word "functional" an uncertainty exists as to the limits of the claim language. How exactly does "functional" limit the claim? This word should be defined or the claim should be limited to those known "functional" gastrointestinal disorders disclosed in the Specification.

2. Claims 1,2, 3, 4, 6, 8 and 18-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. By definition in the Specification on page 2, "The term "alkyl" used alone or as a suffix or prefix, refers to monovalent straight or branched chain hydrocarbon radicals comprising 1 to 12 carbon atoms. An "alkyl" may optionally contain one or more unsaturated carbon-carbon bonds". While applicant may be his or her own lexicographer, a term in a claim may not be given a meaning repugnant to the usual meaning of that term. See *In*

re Hill, 161 F.2d 367, 73 USPQ 482 (CCPA 1947). The meanings given in the Specification is not the usual meaning at all. Alkyl is a group of the formula $-C_nH_{2n+1}$, as is set forth in such sources as Hack's Chemical Dictionary and Hawley's Condensed Chemical Dictionary, or any textbook of organic chemistry. As such it cannot be unsaturated.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claim 15 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Such a utility cannot be deemed enabled.

Pursuant to *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is "undue"; see *In re Vaeck*, 20 USPQ2d 1438, 1444.

The analysis is as follows: The scope of the claim includes treating any or all functional gastrointestinal disorders for which there is no enabling disclosure. Page 12 of the Specification recites "Compounds of the invention are useful for the treatment of diarrhoea, ..., various gastro-intestinal disorders, e.g. constipation, functional gastrointestinal disorders such as Irritable Bowel Syndrome and Functional Dyspepsia, ...".

(A) Breadth of claims.

(a) Scope of the compounds. The instant claim embraces millions of compounds with a benzhydryl piperidine framework with a variation of substituents at three different positions. These variations to the scaffold give a diverse range of compounds, which provide different physical and chemical properties to the compounds of formula (I).

(b) Scope of the diseases covered. Functional gastrointestinal disorders can be defined as any disease or disorder associated with the GI tract, which include the mouth, esophagus, stomach, intestines, rectum and anus. Other organs, such as the spleen, bile ducts, gall bladder, liver and pancreas, can also be a cause of gastrointestinal disorders. As recited, the scope of the claim can include, but is not limited to, tooth decay, periodontal disease, abscesses, canker sores, cold sores, oral cancer, gastroesophageal reflux disease, dysphagia, esophagus cancer, circopharyngeal incoordination, achalasia, diverticula, burning mouth syndrome, pancreas cancer, Crohn's disease, colon polyps, diverticular disease, intestinal parasites, salivary gland disease, sialhorria, dentigerous cyst, glossitis, benign migratory, Ludwig's Angina, Melkerson-

Rosenthal Syndrome, xerostamia, Pierre-Robin Syndrome, diabetes, lactose intolerance, bruxism,ulcerative colitis, cystic fibrosis, pernicious anemia, tropical sprue, cirrhosis, Bassen-Kornzweig syndrome, pancreatitis, Shwachman-Diamond syndrome, anal cancer, acute pancreatitis, anal fissure, anal fistula, colorectal cancer, hemorrhoids, perirectal abscess, proctitis, rectal prolapse, functional constipation, liver cancer, diarrhea, ankyloglossia, Irritable Bowel Syndrome, functional dyspepsia, peptic ulcer, intussusception, Coeliac disease, Whipple's disease, lymphoma, incontinence, chronic pancreatitis, Hirschsprung's disease, infant regurgitation, biliary disorder, hemochromatosis, Wilson disease, tyrosinemia, alpha 1 antitrypsin defiency, glycogen storage disease, primary sclerosing cholangitis, hepatitis A, hepatitis B, hepatitis C, Reyes's syndrome.

(B) The nature of the invention and predictability in the art: The invention is directed toward medicine and is therefore physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(C) Direction or Guidance: That provided is very limited. The dosage range information for treating gastrointestinal disorders is not provided in the Specification. Thus, there is no specific direction or guidance regarding a regimen or dosage effective specifically for gastrointestinal disorders.

(D) State of the Prior Art: These compounds are substituted benzhydryl piperazines with a substitution pattern at two positions. So far as the examiner is aware, no substituted benzyhydryl piperazines of any kind have been used for the treatment of gastrointestinal disorders.

(E) Working Examples: The invention is drawn to the therapy of functional gastrointestinal disorders. There are no working examples or even animal models, in the Specification drawn to this utility to support the use of substituted benzhydryl piperazines to treat any or all functional gastrointestinal disorders.

(F) Skill of those in the art: These diseases and disorders can not be treated generally by any one drug. These are all different diseases and disorders, which occur at different locations and by different modes of action in the body. Hirschsprung's disease, one of the many mentioned above, is a disorder, which is primarily treated with surgery. The instant compounds, substituted benzhydryl piperazines, are recited as useful in treating any or all functional gastrointestinal disorders, for which applicants provide no competent evidence. Coeliac disease is untreatable. Hepatitis is treatable with antiviral agents, a property these compounds not disclosed to have.

(G) The quantity of experimentation needed: Owing especially to the factors of A, C and F, the amount of experimentation is expected to be high.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was

filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

4. Claim16 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Such a utility cannot be deemed enabled.

Pursuant to *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is "undue"; see *In re Vaeck*, 20 USPQ2d 1438, 1444.

The analysis is as follows: The scope of the claim includes treating anxiety for which there is no enabling disclosure. Page 12 of the Specification recites "Compounds of the invention are useful for the treatment of diarrhoea, depression, anxiety, and stress related disorders such as

post-traumatic stress disorders, panic disorders, generalized anxiety disorder, social phobia, and obsessive compulsive disorder, ...".

(A) Breadth of claims.

(a) Scope of the compounds. The instant claim embraces millions of compounds with a benzhydryl scaffold with a variation of substituents at three different positions. These variations to the benzhydryl scaffold give a diverse range of compounds, which provide different physical and chemical properties to the individual substituted benzhydryl scaffold.

(b) Scope of the diseases covered. Anxiety can be defined as a complex combination as negative emotions that includes fear, apprehension and worry and is often accompanied by physical sensation such as palpitations, nausea, chest pain, and/or shortness of breadth.

(B) The nature of the invention and predictability in the art: The invention is directed toward medicine and is therefore physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(C) Direction or Guidance: That provided is very limited. There is no dosage range information in the Specification. Thus, there is no specific direction or guidance regarding a regimen or dosage effective specifically for the therapy of anxiety.

(D) State of the Prior Art: These compounds are substituted benzhydryl piperazines. So far as the examiner is aware, no substituted benzhydryl piperazines of any kind have been used for the treatment of anxiety.

(E) Working Examples: The Applicant has not provided any supporting documents, such as working examples or pharmacological testing, to indicate the said compounds are useful for the therapy of anxiety.

(F) Skill of those in the art: The skills of those in the art haven't established that delta opioid receptor agonists can be used to treat anxiety. Even after the filing date of this case, research shows only the possibility of treating anxiety with a selective delta opioid receptor agonist. "Furthermore, it is possible that δ-opioid-receptor agonists might be novel and potent antidepressants that also have anxiolytic-like effects." See Saitoh et. al. (J. Pharmacol. Sci., 2004, 95, 374-380). This says that as of 2004, the prospect that delta opioid receptor agonists would be anxiolytics is only a possibility, not an established fact.

(G) The quantity of experimentation needed: The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled individual, regarding the pharmaceutical use, for the reasons stated above.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the

claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1, 8, 9, 10, 13, 14 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chang et. al. WO 93/15063.

The current invention teaches substituted diphenyl piperazines, formula (I) for the therapy of pain, where R2= hydrogen, R1 a benzene sulfonamide, and R3 a C1-C6 alkyl. By definition in the Specification on page 2, "The term "alkyl" used alone or as a suffix or prefix, refers to monovalent straight or branched chain hydrocarbon radicals comprising 1 to 12 carbon atoms. An "alkyl" may optionally contain one or more unsaturated carbon-carbon bonds". According to this unconventional definition for alkyl, the allyl moiety falls within the limitations of the definition. Note the R3 variations in claim 7 in the present application.

Chang et. al. teaches several opioid diarylmethylpiperazine compounds for treating analgesia which include generically instant compounds. See pages 10 and 11, formula (II). The definition of various variable groups include: R1= sulfonamides and R6 is hydrogen or C1-C6 alkyl. See page 19, example 110.

Chang et. al. differs from the instant claims in the methyl groups at the 2 and 5 position of the piperzine ring although the substituents at this position can also be hydrogens according to the generically instant compounds of formula (II). See page 10. Thus, the reference teaches that hydrogen and alkyl are alternatively useable for the intended purpose.

Since a methyl group is considered a homolog of hydrogen these compounds are considered equivalent. The MPEP 2144.09 states "Compounds which are position isomers (compounds having the same radicals in physically different positions on the same nucleus) or homologs (compounds differing regularly by the successive addition of the same chemical

group, e.g., by -CH2- groups) are generally of sufficiently close structural similarity that there is a presumed expectation that such compounds possess similar properties. In re Wilder, 563 F.2d 457, 195 USPQ 426 (CCPA 1977).

Claim 20 teaches the process of producing the compound of formula (IX). The process involves reacting the compound formula (VIII) and benzenesulfonyl chloride.

Chang et. al. teaches synthezing 4-(4-allyl-2,5-dimethyl-1-piperidinyl)-((3-benzenesulfonamide)benzyl)-N, N-diethyl benzamide from benzenesulfonyl chloride and 4-(4-allyl-2,5-dimethyl-1-piperidinyl)-(3-amino benzyl)-N, N-diethyl benzamide. See page 98.

Claims 8, 9 and 10 includes the benzene sulfonamide species found in the prior art mentioned above (see Chang et. al. on page 10 and 19). Thus, it would have been obvious to one having ordinary skill in the art at the time of the invention was made to make compounds using the teachings of Chang et. al. and expect resulting compounds to possess the uses taught by the art in view of the equivalency teaching outlined above.

Claims 13 and 14 are drawn to a pharmaceutical composition and for the therapy of functional gastrointestinal disorders, respectively. Chang et. al. teaches the same use, analgesia and gastrointestinal disorders, for the species mentioned above. See page 40 and 43.

6. Claims 5 and 7 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusions

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susanna Moore whose telephone number is (571) 272-9046. The examiner can normally be reached on M-F 8:00-5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Wilson can be reached on (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SM

Mark L. Berch
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